10-Step, Gram-Scale Total Synthesis of (–)-Bipinnatin J

Anthony J. Rodriguez,[†] Maithili S. Pokle,[†] Griffin L. Barnes, Phil S. Baran[*]

ABSTRACT: A concise, scalable total synthesis of (–)-Bipinnatin J is disclosed. Commencing from inexpensive starting materials, this marine diterpenoid was fashioned through a highly convergent synthesis enabled by Ni-electrocatalytic decarboxylative cross–coupling (DCC) taking advantage of succinate as an ethylene 2-carbon bridge, a unique halogen dance-Zweifel sequence to rapidly access a trisubstituted furan, a Ni-mediated 1,6-conjugate addition, and an asymmetric proton transfer.

Furan and butenolide containing cembrenoids (furanocembrenoids) have attracted considerable multidisciplinary interest in the late 20th and 21st century.[1] Within the synthesis community, this is exemplified by the twenty-four (successful and unsuccessful) elegant approaches towards this class of natural products.[2] Biosynthetically, it is evident that Bipinnatin J (**1**, Figure 1) serves as a pivotal intermediate en route to more highly oxidized family members.[3] The furan and butenolide moieties can be subsequently manipulated to produce highly congested, polycyclic frameworks. Indeed, there have been numerous studies and reviews detailing the various proposed biosynthetic interrelationships pertaining to furanocembrenoid-derived natural products (Figure 1A); some of these propositions have been validated in a laboratory setting, such as in the syntheses of Intricarene **2** and Coralloidalide B **3** from **1**.[4] Other family members presumably derived from **1** have remained elusive for decades, such as Bielschowskysin **4** and Lophotoxin **5**, which have accumulated an additional 29 synthetic approaches collectively.[2m–q,5] While **4** has been found to show highly potent and selective anticancer properties based on preliminary biological evaluation, **5** has undergone much more extensive study and implementation as an irreversible neuromuscular acetylcholine antagonist.[1b,6] This communication delineates our inaugural entry into this class of natural products culminating in a concise (10-step), scalable (single-pass, gram-scale), enantioselective, convergent preparation of **1** enabled by powerfully simplifying Ni-catalyzed C–C bond forming reactions.

As **1** represents a potentially useful starting point to access numerous polycyclic, furanocembrenoid-derived marine natural products, rapid gram-scale access through total synthesis is essential as semi-synthesis is not currently a sustainable option. The retrosynthetic analysis described herein for **1** benefitted from the wisdom of four prior elegant syntheses.[2c–f] Foremost amongst the invaluable insight gained from those studies was the use of a highly effective NHK macrocyclization (first reported by Paquette to prepare similar structures).[7] The use of this disconnection necessarily leads one back to the common acyclic bis-furan precursor **6**, deliberately

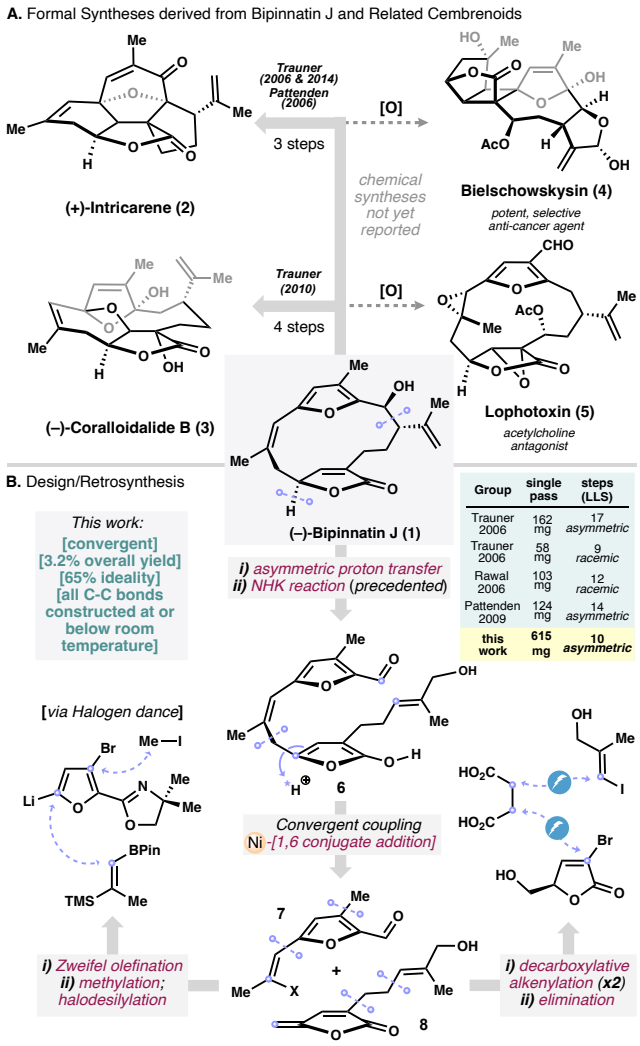
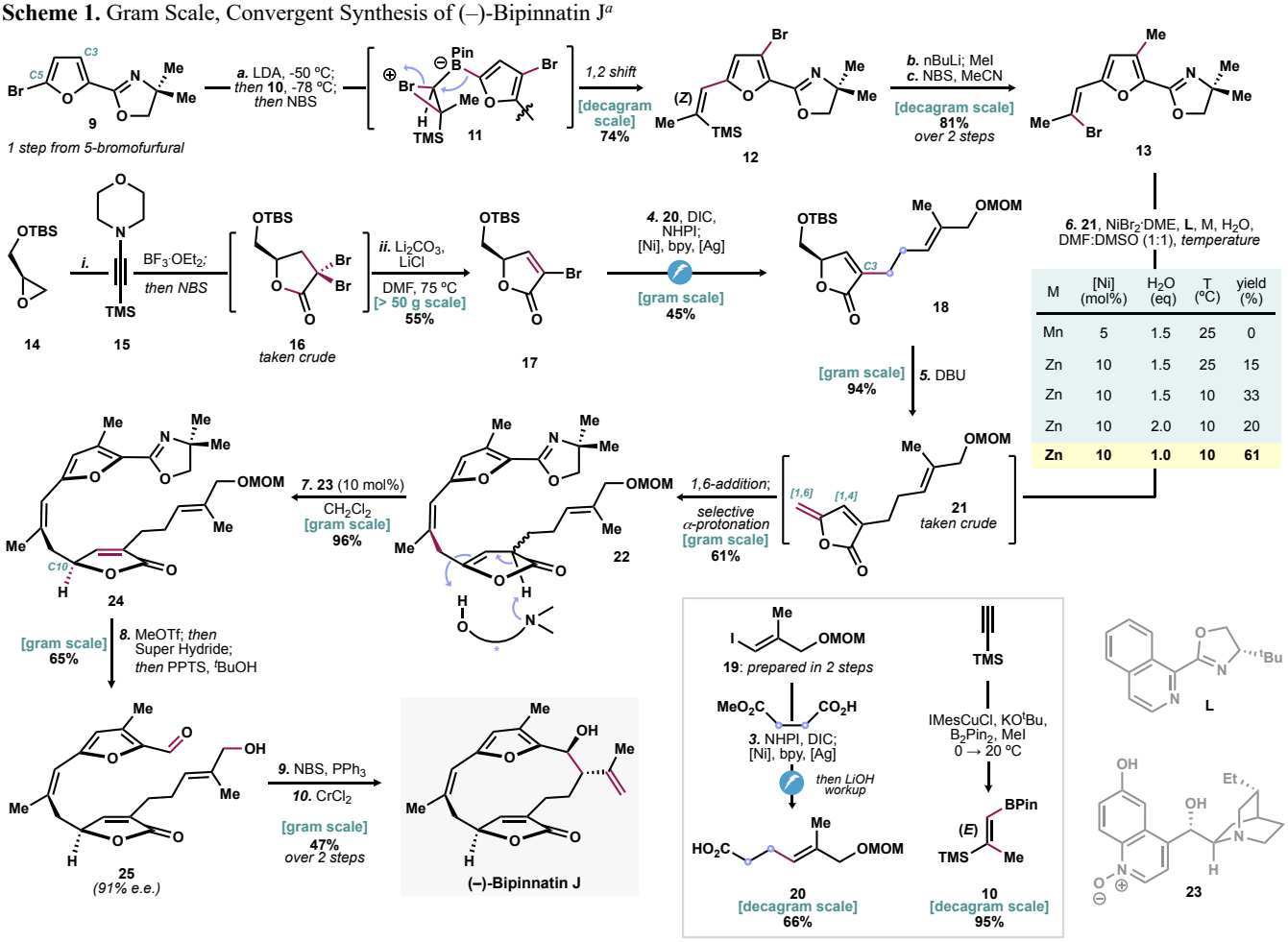


Figure 1. Bipinnatin J (**1**): (A) formal syntheses derived from **(1)** and related cembrenoids; (B) design/retrosynthesis.

Scheme 1. Gram Scale, Convergent Synthesis of (–)-Bipinnatin J[a]



[a] For detailed reagents and conditions, see Supporting Information.

depicted as its hydroxyfuran tautomer. An asymmetric protonation event was envisaged to set the key butenolide stereocenter present in **1**. Disconnecting **6** into roughly equal halves leads to building blocks **7** and **8**. In the forward direction, a chemoselective conjugate addition of **7** onto **8** would be required. The trisubstituted furan fragment **7** might arise through a unique sequence of tandem halogen dance/Zwiefel olefination eventually leading back to inexpensive bromofurfural. Finally, a strategy using succinate as a linchpin ethylene source to link two alkenyl halides was imagined using recently developed Ni-electrocatalytic decarboxylative cross–coupling (DCC) to access fragment **8**.

The synthesis, outlined in Scheme 1, commenced with construction of the required trisubstituted furan **13**. Beginning from 5-bromofurfural, a condensation reaction produces furyl oxazoline **9** on multi-decagram scale (see SI for details). This sets the stage for a strategic halogen dance maneuver, wherein a directed deprotonation at C3 triggers Li migration to the more stabilized C5 position after subsequent lithium halogen exchange.[8] This intermediate was trapped with alkenyl boronic ester **10**, which was derived from TMS-acetylene through a high-yielding, scalable Cu-borylation reaction.[9] This gives rise to an intermediate boron-ate species, which was then treated with NBS to effect formation of a bromonium ion **11** that triggers a facile 1,2-shift to effect Zweifel olefination. Importantly, this powerful and scalable transformation (conducted on decagram scale) proceeded with complete inversion of configuration to produce alkenyl furan **12**, which contained the required (*Z*)-stereochemistry present in **1**. After a straightforward methylation at C3 using ^{n}BuLi and methyl iodide (98% yield), the alkenyl silane served as a surrogate for an alkenylhalide via halodesilylation. Concerns that such a reaction would cause significant reversion of configuration of the alkene product back to (*E*) were unfounded as a satisfactory 5:1 ratio of easily separated products favoring (*Z*)-alkenyl bromide **13** resulted from treatment with NBS in acetonitrile (83% yield). The protocol listed above was used to prepare >15 grams of **13** thus far. The approach outlined above may be a generally useful strategy to procure highly substituted furans from furfural-based feedstocks.

Next, the synthesis of requisite butenolide **18** was carried out. Beginning from (*R*)-TBS-glycidol **14**, methodology developed by the Jacobsen group was enlisted to deliver bromobutenolide **17**.[10] Thus, treatment of **14** with ynamine **15** (commercially available) in the presence of BF_3•OEt_2 effects formation of a highly reactive α-silylenamine that reacts in situ with NBS, producing gem-dibromo-γ-lactone **16** (not isolated), which is smoothly eliminated in crude form (treatment with Li_2CO_3, LiCl, 75°C) to produce **17** in 55% isolated yield overall. This sequence proved to be highly efficient, being performed

routinely to produce >40 grams of product over two steps. At this juncture a Ni-electrocatalytic C(sp^2)-C(sp^3) DCC was invoked to access **18**, necessitating the preparation of unsaturated acid **20**.[11] Towards this end, MOM-protected (*E*)-alkenyl iodide **19** (accessed in two steps involving carboalumination and MOM-protection) was prepared on large scale (> 100 g, see SI for details). This material was subsequently coupled with mono-methyl succinate through Ni-electrocatalytic DCC alkenylation. After electrolysis and during work-up the methyl ester intermediate (not shown) was readily saponified with aqueous lithium hydroxide, giving rise to homoallylic acid **20.** As a testament to the robustness of this methodology, this reaction was highly amenable to scale up – routinely being conducted on a > 10 gram scale using a jar as the reaction vessel and being run completely open to air. With copious quantities of **20** in hand, DCC between **17** and **20** produced C3-alkylated butenolide **18** in 45% isolated yield (gram scale). For this DCC, *N*-methylpyrrolidinone (NMP) instead of DMF as the solvent was crucial, as was the implementation of 5 mol% LiCl as an electrolyte to effect voltage stability (other electrolytes and higher loadings of LiCl proved to be highly deleterious to these reactions). The overall sequence from alkenyl iodide **19** to butenolide **18** is notable as succinate serves as an ethylene source to bridge different sp^2-components.

Whereas **18** is a bench-stable substrate, repeated attempts to utilize derivatives of the protected primary alcohol in subsequent couplings were plagued by immediate elimination to unsaturated butenolide **21** (see SI for details). This inherent tendency to eliminate was embraced as described below. In fact, clean elimination of the -OTBS functionality with DBU delivered nearly quantitative yield of **21**. This set the stage for a pivotal sequence involving 1,6-conjugate addition followed by asymmetric proton transfer.

With both fragments (**13** and **21**) in hand, we began to coax their union in a way that would result in selective 1,6-conjugate addition. Critical to the success of this strategy was the formation of the β,γ-unsaturated isomer **22** rather than the α,β-unsaturated congener due to the ensuing asymmetric proton transfer (*vide infra*). Conventional Cu-mediated conjugate additions showed complete selectivity for 1,6 versus 1,4 addition albeit in low yield (10–46%). This classic approach suffered from a lack of reproducibility and labor-intensive, multi-stage processes that necessitated the usage of *tert*-butyl lithium in order to affect cupration. Extensive attempts to improve this chemistry (see SI for a summary) ultimately inspired exploration of a more modern solution to this problem which involved investigating various metals to carry out a direct conjugate addition (Pd, Zn, Ti, Cr, Co, etc.). The Ni-catalyzed conjugate addition methodology recently reported by Zhou and co-workers was particularly exciting in this regard.[12] Indeed, initial hits with their reported conditions were promising and after a few rounds of optimization (see inset table for brief summary and SI for full optimization) the targeted reaction could be accomplished on gram scale (61% yield) delivering the desired product **22** through concomitant C3-protonation (> 10:1 selectivity). This powerful technology benefits from non-cryogenic temperature, a lack of highly reactive/corrosive materials (organolithium, cyanide, etc.), and its practicality in terms of set-up.

At this stage, a pivotal asymmetric proton transfer was required to restore the stereochemistry at C10. Towards this end, Deng's pioneering asymmetric proton transfer methodology performed flawlessly.[13] Thus, treatment of **22** with 10 mol% of Cinchona alkaloid-derived quinoline-*N*-oxide **23** cleanly effects the desired 1,3-isomerization producing conjugated butenolide **24** in nearly quantitative yield (gram-scale). Concerned that racemization might occur during a required reduction/deprotection sequence, determination of enantiopurity was delayed. With the near-complete carbon skeleton of **1** in hand, the oxazoline ring that served essential roles (aldehyde surrogate, directing group) was disassembled in chemoselective way. This one-pot sequence was accomplished by: (1) quaternization of the oxazoline moiety (MeOTf), (2) treatment with lithium triethylborohydride (Super Hydride®), and (3) subsequent PPTS-mediated hydrolysis of both the intermediate oxazolidine and allylic-MOM-ether to afford aldehyde **25** in 65% yield (gram-scale); this material's enantiopurity was determined as being 91% e.e., suggesting that Deng's methodology indeed proceeded asymmetrically and the subsequent transformations resulted in negligible enantio-erosion. This constituted a formal total synthesis of (–)-**1**, as Trauner reported there to be no further enantio-erosion during the required final steps.[2e] The reported end-game protocol was applied (Appel reaction followed by diastereoselective NHK macrocyclization) to deliver > 600 mg of **1** in a single pass. Although these last two reactions are known, it is worth noting that we have now performed each of them on gram-scale, observing only slight variations in isolated yield and reported diastereoselectivity. The route described herein to access **1** could, in principle, be executed by two chemists in about 10 days starting from commercial materials.

Although the synthesis of (–)-**1** is the shortest route disclosed thus far, one potential critique is that the chirality purchased from glycidol derivative **14** is ablated (**18** to **21**) and then reinstalled through asymmetric proton transfer (**22** to **24**). However, attempts to utilize derivatives of **18** in direct coupling almost always led to **21** and, from an efficiency standpoint, offered no advantage in step count as the TBS group needed to be removed and the primary alcohol functionalized further.

A convergent, scalable (single pass, gram-scale), concise (10-steps, LLS) approach to (–)-Bipinnatin J **1** was achieved in a 3.2 % overall yield and with 65% ideality (see SI for calculation) from simple building blocks. Unique features of this synthesis include: (1) formal ethylene insertion made possible through sequential Ni-electrocatalytic DCC to stitch together C-sp^2 and C-sp^3 units, (2) a unique halogen dance-Zweifel olefination maneuver to access a highly differentiated, triply-substituted alkenyl furan, (3) a Ni-catalyzed 1,6-addition onto a γ-methylidene butenolide producing predominantly β,γ-butenolide isomer, and (4) demonstration of Deng's asymmetric 1,3-proton transfer in complex synthesis. These strategies may find more general utility for the modular syntheses of trisubstituted furans, chiral α,γ-substituted butenolides, and carbon frameworks using inexpensive succinates.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and analytical data (PDF)

AUTHOR INFORMATION

Corresponding Author

Phil S. Baran − Department of Chemistry, Scripps Research, La Jolla, California 92037, United States; orcid.org/0000-0001-9193-9053; Email: pbaran@scripps.edu

Authors

Anthony J. Rodriguez – Department of Chemistry, Scripps Research, La Jolla, California 92037, United States. https://orcid.org/0009-0002-1119-0551

Maithili S. Pokle – Department of Chemistry, Scripps Research, La Jolla, California 92037, United States. https://orcid.org/0009-0004-0412-0584

Griffin L. Barnes – Department of Chemistry, Scripps Research, La Jolla, California 92037, United States. https://orcid.org/0000-0002-5731-4380

Author Contributions

† A.J.R. and M.S.P. contributed equally to this work.

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GRAPHICAL ABSTRACT